C BT 12.12

a2 Claim 55 (amended) A method for administering a fatty acid-taxane conjugate in a polyoxyethylated castor oil to a subject in need of such treatment, comprising infusing the conjugate in fewer than 3 hours.

a3 Claim ~~69~~ 13 (amended) An injectable composition of at least one fatty acid-taxane conjugate in a polyoxyethylated castor oil, comprising less than about 0.3 mg/ml of the at least one fatty acid-taxane conjugate.

a4 Claim ~~82~~ 17 (amended) The fatty acid-taxane conjugate composition of claim ~~70~~ 14, wherein the surfactant is a polyoxyethylated castor oil [Cremophor EL or EL-P].

a5 Claim ~~90~~ 20 (amended) The fatty acid-taxane conjugate composition of claim ~~84~~ 18, wherein the surfactant is a polyoxyethylated castor oil [Cremophor EL or EL-P].

a6 Claim ~~103~~ 24 (amended) The fatty acid-taxane conjugate composition of claim ~~97~~ 22, wherein the solvent is a polyoxyethylated castor oil [Cremophor EL].

a1 Claim ~~108~~ 26 (amended) The fatty acid-taxane conjugate composition of claim ~~107~~ 25, wherein the surfactant is a polyoxyethylated castor oil [Cremophor].

REMARKS

Claims 48, 55, 69, 82, 90, 103 and 108 were amended. No new matter has been added.

The Examiner has rejected pending claims under 35 U.S.C. §103 as being unpatentable over Mayhew or Bradley in view of Agharkar. The Examiner also has rejected the pending claims under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-6 of U.S. Patent No. 5,919,815. Applicants respectfully traverse these rejections. Applicants believe that the Examiner has not made out a *prima facie* case for rejecting the claims, as explained in greater detail below.

It is perhaps useful to describe several aspects of the present invention as background for discussion about the various independent claims presented. The invention is based on several surprising discoveries. A major aspect of the invention involves the unexpected finding that higher concentrations of anticancer drugs can be delivered to human subjects than ever before expected. The dose-limiting toxicity of the anticancer drug is altered due to its conjugation to the fatty acid. This has profound implications on anticancer therapies.

At the time of filing the present application, it was unclear to applicants why applicants could deliver substantially higher doses of an anticancer compound to a subject if the anticancer compound was conjugated to a fatty acid. It appears, in retrospect and based upon experiments

carried out after the filing of the present application, that the fatty acid is causing the anticancer compound to be selectively accumulated in the rapidly growing cancer cells. Perhaps this is because fatty acids might be an important component (such as a building block or a nutrient) to rapidly-proliferating cells. The net effect is that more drug is sequestered selectively in the cancer cells and less drug is available in other tissues, thereby reducing the dose-limiting toxicity of the anticancer compound.

Protarga, Inc., the assignee of the present invention, is having conducted at Johns Hopkins a clinicial trial relating to a conjugate of docosahexaenoic acid and paclitaxel. To date, the researchers at Johns Hopkins have been able to administer more than four times the amount of paclitaxel to human beings than has ever been used before clinically. Not withstanding this, there has been no dose-limiting toxicity observable at such doses. In fact, certain of the side-effects typical of administration of paclitaxel in clinical doses have been absent, such as loss of appetite and loss of hair. This is despite administering four times the molar amount of paclitaxel to the patients.

Another surprising aspect of the invention is the ability to solubilize much higher concentrations of the conjugates of the invention in surfactants such as polyoxyethylated castor oils than is possible for anticancer compounds which are not conjugated to fatty acids. For example, applicants can routinely obtain 40 mg/ml or more of the docosahexaenoic acid-paclitaxel conjugate in a 50%/50% Cremaphor/ethanol co-solvent system, whereas the prior art typically is at 6 mg/ml of paclitaxel in the same co-solvent system.

Another surprising aspect of the invention is the ability to dissolve conjugates of taxanes and fatty acids in ethanol at very high concentrations, e.g., 100 mg/ml. The conjugates are very stable when stored in ethanol in that manner.

Another surprising aspect of the invention is the ability to administer higher concentrations of the conjugates of the invention (than the unconjugated anticancer drug) and in shorter durations. For example, currently 0.3-1.2 mg/ml of paclitaxel in 10%/10% Cremaphor/ethanol is administered over at least 3 hours. The present invention permits much higher concentrations of the fatty acid-taxane conjugates and in less than 3 hours.

The foregoing unexpected results are embraced by the rejected claims. For example, method claims 17, 21, 23, and 28 describe administering fatty acid-anticancer compound conjugates in amounts which far exceed the maximum tolerated dose for the unconjugated

anticancer compounds. Claim 33 describes a kit for carrying out the method of claim 17. Claim 1 describes a formulation in a container for administration to a subject, wherein the container contains the amount of conjugate necessary for carrying out the method described in claim 17. Other aspects of the invention are featured in other of the independent claims.

The claimed invention is not shown or suggested by any of the cited prior art.

The Prior Art

The Mayhew patent teaches, among other things, fatty acid-taxane conjugates for treating cancer. Mayhew specifically attempts to avoid the use of the prior art Cremaphor vehicles. This is described in column 1, lines 53-67 where Mayhew indicates that the Mayhew conjugates can be formulated with lipid carriers and can avoid the use of polyoxyethylated castor oils such as Cremaphor.

Applicants wish to focus the Examiner's attention on several specific teachings of Mayhew. First, Mayhew specifically teaches administering the conjugates of Mayhew in amounts that are the same as or less than the amounts used when administering the unconjugated anticancer compounds. See column 9, lines 50-67 and column 12, lines 52-67. Thus, Mayhew teaches away from a main feature of the present invention, that is, the administration of anticancer compounds as conjugates in amounts which far exceed the maximum tolerated dose of the anticancer compound unconjugated.

Mayhew also specifically is directed to avoiding the use of Cremaphor. Mayhew, therefore, in this aspect teaches away from those particular compositions of the present invention which involve Cremaphor and similar surfactants.

Finally, it is noted that Mayhew does not mention anything about storage of the conjugates described in Mayhew in ethanol.

The Bradley patent has overlapping inventorship with the present application. It is noted that the Bradley patent simply states with respect to the fatty acid-taxane compositions described and claimed, that such compositions are formulated and used according to art-recognized methods. Bradley does not mention or suggest administering the conjugates in amounts that exceed the maximum tolerated dose of the unconjugated anticancer compound. Bradley does not mention or suggest storage of the conjugates at high concentrations in ethanol. Bradley does not mention or suggest the possibility of high concentrations of the conjugates in Cremaphor.

The Agharkar patent teaches in general that paclitaxel is unstable in ethanol/Cremaphor solutions. Agharkar teaches that the instability during storage is due to an unwanted activity in the Cremaphor, that is, carboxylate anions. Agharkar teaches that the Cremaphor can be treated with an aluminum oxide bed to separate such ions or that an acid can be added to Cremaphor to inactivate such ions, thereby protecting the paclitaxel against decomposition by the unwanted activity of the Cremaphor.

The Agharkar patent adds nothing to the prior art regarding how much taxol to give a subject or how much taxol to put in a kit or container for administration to a subject. Agharkar teaches to use paclitaxel as described in the prior art, except to store it after deactivating the carboxylate anions.

The Examiner Has Not Made Out a *Prima Facie* Case For Rejecting the Claims

Respectfully, none of the references teach or suggest the novel aspects of the invention which are embraced by the independent claims. It therefore is believed that the Examiner has not made out a *prima facie* case for rejecting the claims. To summarize, none of the references show or suggest:

- injectable formulations, methods and compositions for administering a fatty acid-anticancer compound in an amount that is much greater than the maximum tolerated dose for the unconjugated anticancer compound (claim 1, claim 17, claim 33, and claim 57)
- injectable compositions containing high concentrations of fatty acid-taxane conjugates (claim 57, claim 84, claim 97 and claim 110)
- compositions containing fatty acid-taxane conjugates at high concentrations in surfactants such as Cremaphor (claim 70 and 84)
- compositions containing high concentrations of fatty acid-taxane conjugates in solvents such as ethanol (claims 97 and 110).

It is also believed that the Examiner has not made out a *prima facie* case for rejecting the claims because the references are not combinable in the manner suggested by the Examiner. Mayhew specifically teaches away from using Cremaphor. Mayhew indicates that Cremaphor can be avoided by using the conjugates of Mayhew and that avoiding Crempahor is desirable. This teaches away from combining Mayhew (or Bradley, for that matter, which shows a

conjugate similar to those disclosed in Mayhew) with Agharkar which is directed to the use of Cremaphor.

It is believed that the Examiner also has not made out a *prima facie* case for rejecting the claims because the Examiner has misstated the teaching of the Agharkar patent. The Examiner states that Agharkar teaches in columns 1 and 2 that polyoxyethylate castor oil improves the bioactivity of taxanes. Applicants disagree. Agharkar teaches that Crempahor can reverse the multi-drug resistant phenotype of tumor cells and can increase hemopoesis. Agharkar also teaches, however, that Cremaphor can result in particulates forming upon dilution within fusion solutions and that Cremaphor can decrease the pharmaceutical activity of paclitaxel by as much as 60%. Finally, Agharkar teaches nothing about fatty acid-taxane conjugates. Thus, it is not believed that Agharkar stands for the proposition that those of ordinary skill in the art would combine Cremaphor with anticancer agents (including taxanes) for "improved bioactivity" as suggested by the Examiner.

Finally, it is also believed that the Examiner has overlooked the unexpected results described in the application.

The specific issues of obviousness, assuming a *prima facie* case has been made out, is whether there is a sufficient showing to rebut such a *prima facie* case. It is applicants' position that even if a *prima facie* case has been made (which applicant disputes), applicant can demonstrate (as alleged in the application) that applicants' claimed compounds and related methods result in biological activities which were unexpected and which could not have been predicted by those of ordinary skill in the art. These unexpected results are persuasive evidence that applicants' claimed compositions have nonobvious properties. Since a claimed composition and its properties are inseparable in patent law, the claimed composition and related methods would not have been obvious at the time the invention was made to a person having ordinary skill in the art.

The Court of Appeals for the Federal Circuit has stated recently that when an applicant "demonstrates substantially results, ...", and states that the results were unexpected, it should suffice to establish unexpected results in the absence of evidence to the contrary (*In re Soni*, 54 F3d 746 (Fed. Cir. 1995)). The Examiner as not provided any basis to question the applicants' statements about unexpected properties. Accordingly, there is no reasonable basis to doubt that applicant has established unexpected results for the claimed compounds and related methods.

The Examiner also rejected the claims under the judicially created doctrine of obviousness-type double patenting over Bradley. Respectfully, again it is believed the Examiner has not made out a prima facie case for rejecting the claims. The claims include limitations that are neither shown nor suggested by Bradley. These differences are outlined above. It is believed that this rejection is improper and that it should be withdrawn.

Applicants wish to point out that if the Examiner finds any of the independent claims allowable, then applicants would like the opportunity to add back to the application the claims which were dependent from such independent claim as originally filed. Likewise, if the Examiner does not believe that the present response is adequate to distinguish the claims over the cited references, then applicant requests the opportunity to meet with and interview the Examiner in connection with this case in order to advance prosecution.

Respectfully submitted,

Edward R Gates

Edward R. Gates, Reg. No. 31,616
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210-2211
(617)720-3500

Attorney Docket No: N0260/7031
April 11, 2000
X 4/12/00